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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,749	01/16/2004	Cathlin Marie Biwersi	PC25403A	8348

28940 7590 08/04/2006

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,749	BIWERSI ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/27/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I drawn to unfused pyrimidine in the reply filed on 5/1/2006 is acknowledged. Claims 1-17 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants' traversal of the restriction requirement is not persuasive for reasons of record. The traversal is on the ground(s) that the search and examination of all groups is not burdensome and that breaking Markush group is improper. This is not found persuasive. As for the traversal the following apply.

1. First of all, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(i)); and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(i), § 808.01(a), and § 808.02).

Both these criteria are to be met with.

Contrary to applicants' urging, both the criteria of distinct and independent and serious search burden were not met with. Invention and search burden are clearly presented in the previous office action. To summarize, principles of classification dictate that ring structures with different ring sizes and having different numbers of heteroatoms to be classified in different classes. Such classification, as noted in the previous office action, stems from the fact that the ring structures have different properties, different reactivities and different effects on the substituents. They are made and used differently. In the instant case, the there are several hetero rings embraced in the instant claims such as unfused pyrimidines, bicyclopyrimidines, 1,3,5-triazines, 1,2,4—bicyclotriazines, bicyclopyridazines, bicyclopyrazines, pyridines and bicyclopyridines cores. Prior art does not teach these cores are equivalent. Hence, each invention is distinct and independent. Furthermore, applicants have not asserted that the core groups are all equivalent. In which case, prior art, which anticipates instant elected invention, may then render the non-elected inventions as obvious variant and can thus be applied.

2. Applicants' argument that there is no serious search burden to examine all said groups is totally incorrect. First of all, as noted above, they are directed to structurally dissimilar compounds that lack common core. Consequently, the groups have different classifications and require separate prior art searches. It is mandatory for the examiner to search all classes and subclasses. Contrary to applicants' urging it would not be possible with the limited fixed time available for the examiner to examine each case with

thorough search. Searching all possible classes and subclasses embraced by the generic and specifically recited core would of serious search burden.

3. Examiner also noted in the previous office action "Should applicant traverse on the ground that the core species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention". Applicants have not asserted that the all groups are not distinct and they are all equivalent. Applicants have not submitted evidence or identified such evidence now of record showing the core group to be obvious variants or clearly admitted on the record that all core groups embraced in the instant inventions are equivalent. In which case examiner needed not search all cores. A prior art which anticipates any one of the groups embraced by a specific core (i.e. choices of I, II,III) may then render rest of the core groups as obvious variant. In other words, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In want of such assertion or evidence, searching the entire core would be serious search burden.

Applicants have argued that the above two criteria set forth in MPEP as noted above is not applicable to instant case as they involve Markush group. The passage MPEEP 803.02 clearly states as quoted by the applicants that even such cases that is

even if the inventions are distinct and independent there should not be any serious search burden. See last paragraph of the response.. As noted above searching all the cores heterocyclic groups would be serious search burden.

Apparently applicants appear to lack understanding of the Search process and search burden. Applicants have asserted that it is not a search burden to search all cores namely, unfused pyrimidines, bicyclopyrimidines, 1,3,5-triazines, 1,2,4—bicyclotriazines, bicyclopyridazines, bicyclopyrazines, pyridines and bicyclopyridines cores in a single search. This lacks factual support.

Examiner has to search a commercial database-STN-CAPLUS for structure search and also have to search patent literature database- EAST and or West. These two are mandatory. In addition, it is essential to search NPL database.

In the instant case, the structure search in CAPLUS would involve searching as unfused pyrimidine, bicyclopyrimidine, 1,3,5-triazine, 1,2,4—bicyclotriazine, bicyclopyridazine, bicyclopyrazine, pyridine and bicyclopyridine core compounds which should also include multiple variable substituents. Such a search would never run to completion as it would exceed one million or more compounds upper limit set forth for in Registry file.

Without completion of the search it is not possible to perform further search and examine. In addition, to this search, examiner has classified and searched all controlling cores based on the elected subject matter to cover the full scope of the elected claims. This includes varius heterocyclic substituents. To illustrate the extent of search burden, if one were to search class 544, which includes six membered

heterocyclic rings with two or more hetero atoms, embraced by triazine and pyrimidine, the east database has 12885 patents. This would be a serious burden to search. In the instant case, in addition one has to search class 546 for pyridine besides composition class 514 for all these cores.

In order to further reduce burden USPTO classification provides distinct subclasses related each distinct heterocyclic core. Even with such subclasses variation in substituents patterns results more than one subclass to search and thus leads to serious search burden if all heterocyclic cores are to be searched. This is shown in the Search note where all such classes/subclasses related to the elected subject matter is searched and reviewed for applying prior art. It should be self evident that the number patents to searched is too many to justify that the search is indeed a serious burden in the instant case.

Applicants also have argued that invoking In re Weber and In re Harnish that the restriction requirement is improper. Again, this argument is not persuasive and the case laws cited are not the point. Careful analysis of the case laws will show that there is condition clause that unity of invention should be considered. To quote MPEP 803 'Since the decisions In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, **unless the subject matter in a claim lacks unity of invention.** In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). **Broadly, unity of invention exists where compounds included within a Markush**

group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

First of all, the instant application is not 371 of PCT application entering national stage. It is a US application and that the only criteria for restriction are as stated above, whether the inventions are independent and distinct and whether the search is a serious search burden. As noted above, instant inventions fail to meet both these conditions.

Secondly, applicants have not shown what portion of the core share a substantial structural feature disclosed as being essential to that utility.

Thirdly, applicants have not even made the all the core compounds and therefore it would hard to say that they share the same utility.

Fourthly, the patent literature and references provided by the applicants in IDS clearly shows some of the structurally related compounds not claimed in the instant claims have different utility. In fact some of the trisubstituted triazines are known have different utility such fire retardants. This would negate the common utility requirement of the substantial structural feature.

Based on the foregoing reasons, the requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 12/27/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim ,not specifically rejected, is rejected as it is dependent on a rejected claim and shares the same indefiniteness.

1. Recitation of "pharmaceutically acceptable salts, esters, amides and prodrugs in claim 1 renders claim 1 and its dependent claims indefinite as it is not clear whether claim 1 is a compound claim or a composition containing the compound of formula I and its pharmaceutically acceptable salts, esters, amides and prodrugs.

Note Markush recitation should be alternate form and in singular whenever applicable.

2. Recitation of " esters , amides and prodrug thereof" in claim 1, renders claim 1 and its dependent claims indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups embraced in X, W, Y, A^1 and R^1 include such groups, namely esters, amides, alkoxycarbonyl etc. Therefore it is not clear what is the difference between these variable groups and the esters, amide and prodrug groups recited in the last line of the claim 1. There is a clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound

bearing the variable group would be deemed as inactive which is not what the claim recites.

Note claim 11 is included in the rejection as it is not clear the ester function in these claims result in a prodrug or active compound.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1-8. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrug of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection

have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The direction concerning the prodrug is found in page14, lines 20-25. There is no working example of a prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph

spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is

clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 12-17 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating rheumatoid arthritis and breast cancer does not reasonably provide enablement for treating any abnormal cell proliferative disease, any cancer, any inflammatory diseases, any autoimmune diseases, any neurodegenerative diseases, any DNA viral infections, and any RNA viral infections specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

The instant method of use claims 12-17, are drawn to treating any abnormal cell proliferative disease, any cancer, any inflammatory diseases, any autoimmune diseases, any neurodegenerative diseases, any DNA viral infections, and any RNA viral infections by inhibiting Cyclin Dependent kinases or FGR kinases in general. Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of kinase by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of CHK and FGR kinase, based on limited assay, it is claimed that inhibiting any or all kinases and treating any or all diseases including any or all cancers in general, which there is no enabling disclosure. The scope of the claims includes any or all cancer or treating any abnormal cell proliferative disease, any cancer, any inflammatory diseases, any autoimmune diseases, any neurodegenerative diseases, any DNA viral infections, and any RNA viral infections including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 1-2, and 61-62. The instant compounds are disclosed to have CDK and FGR kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as kinase inhibitor that would be useful for all sorts of proliferative diseases and cancers, autoimmune diseases, any inflammation or any autoimmune disease, any neurodegenerative disease any DNA viral infection and any RNA viral infection which involve signal transduction pathway of these kinases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as

psoriasis and cancers, autoimmune diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the thousand of diseases embraced by the terms abnormal cell proliferative disease, cancer, inflammation, and autoimmune disease, neurodegenerative disease, Any viral infections caused by DNA and OR RNA virus or the unknown list of "diseases associated with signal transduction pathways operating through CDK or FGR kinase.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

In addition, the scope of the claims includes treatment of various viral diseases due to DNA virus such as hepatitis B virus, herpes viruses (e.g., Herpes Simplex Virus, Cytomegalovirus (CMV), Epstein-Barr Virus, (EBV)), smallpox virus, or human papilloma virus (e.g., HPV), many human and animal pathogens: flaviviruses, such as dengue fever, West Nile, and yellow fever; pestiviruses, such as bovine viral diarrhea (BVD), and hepaciviruses, such as hepatitis C; filoviruses such as ebola; parainfluenza viruses, including respiratory syncytial; rubulaviruses, such as mumps; morbillivirus, such as measles, picomaviruses, including the echoviruses; the coxsaclçieviruses; the polioviruses; the togaviruses, including encephalitis; coronaviruses, including Severe Acute Respiratory Syndrome (SARSI; rubella; bunyaviruses; reoviruses, including rotaviruses; rhabdoviruses; arenaviruses, such as lymphocytic choriomeningitis, as well as other RNA viruses of man and animal.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for

proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Mass, R. D., Int. J. Radiation Oncology Bio. Phys. Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002. Also see Daifuku Biodrugs17(3); 169-177, 2003. and Anderson etal., Annu. Rev. Microbiol., 58:183-205, 2004 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require protein kinase inhibitory activity.

2) The state of the prior art: A publication expressed that the protein kinase inhibition effects are unpredictable and are still exploratory. See Mass, R. D., and Fabbro et al., Daifuku and Anderson etal., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of protein kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all proliferative diseases and cancers including those yet to be related to protein kinase.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from

8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

7/20/2006